

EPI-00672

PATENT

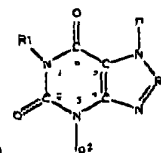
Marked-up Claims

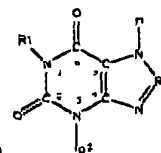
108. (Amended) A pharmaceutical composition comprising [,] a carrier; a nucleic acid in the form of an aerosol that comprises one or more oligonucleotide(s) (oligo(s)) effective to alleviate hyper-responsiveness to, and/or increased levels of, adenosine, bronchoconstriction, lung allergy(ies) and/or inflammation, and contains up to and including about 15% adenosine (A), the oligo being anti-sense to an initiation codon, a coding region or a 5' or 3' intron-exon junctions of a gene encoding an adenosine [A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> or A<sub>3</sub>] A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> or A<sub>3</sub> receptor or anti-sense to their respective mRNA, pharmaceutically and veterinarily acceptable salts of the oligo(s) or mixtures thereof; and a surfactant that may be operatively linked to the nucleic acid.

113. (Amended) The composition of claim 108, wherein the oligo is anti-sense to the initiation codon of the mRNA, to the 5' or 3' intron-exon junctions or to sequences of the coding region comprising 2 or more G and/or C of the adenosine [A<sub>1</sub>] A<sub>1</sub> receptor gene.

115. (Amended) The composition of claim 108, wherein if the oligo contains adenosine (A), at least one A is substituted by a universal base selected from the group consisting of heteroaromatic bases [which] that bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A<sub>1</sub>, A<sub>2b</sub> and A<sub>3</sub> receptors, and heteroaromatic bases [which] that have no activity or have [an] agonist activity at the adenosine A<sub>2a</sub> receptor.

119. (Amended) The composition of claim 118, wherein the pyrimidines or purines are selected from theophylline, caffeine, dyphylline, etophylline, acephylline piperazine,



bamifylline, enprofylline or xantine [having the chemical formula , wherein R<sup>1</sup> and R<sup>2</sup> are independently H, alkyl, alkenyl or alkynyl and R<sup>3</sup> is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, NH<sub>2</sub>-alkylamino-ketoxyalkyloxy-aryl or mono or dialkylaminoalkyl-N-alkylamino-SO<sub>2</sub> aryl].

130. (Amended) The composition of claim 108, wherein the surfactant is selected from surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D, [and] surfactant protein D or active fragments thereof, non-dipalmitoyl disaturated phosphatidylcholine, dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphandylinositol, phosphatidylethanolamine, phosphatidylserine,

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COND  
SUB 05  
COND

phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholine, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycerol-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate, lamellar bodies, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitic acid, non-ionic ethylene and/or propylene oxide block copolymers, polyoxypropylene, polyoxyethylene, poly (vinyl amine) with dextran and/or alkanoyl side chains, polyoxy ethylene ethers, phenoxy polyethoxy alcohols, phosphatidyl choline esters, [and] phosphatidyl ethers, palmitates, [alcohols] tyloxapol, phospholipids, [neutral lipids,] fatty acids, [or] surfactant-associated proteins or  $C_{22}H_{42}O_2$ .

SUB 06  
M 6

137. (Amended) The composition of claim 136, comprising a pharmaceutically or veterinarily acceptable carrier, the nucleic acid, a surfactant, and other therapeutic agents [a therapeutic agent selected from adenosine A1, A2b or A3 receptor activity inhibiting agents other than the oligo(s), anti-arrhythmic agents, anti-inflammatory agents, anti-bacterial agents, anti-sepsis agents, adenosine or agents exhibiting adenosine agonist activity, analgesics, diuretics, kidney activity maintenance or restoration agents or agents for the treatment of pulmonary vasoconstriction, inflammation, allergies, asthma, acute respiratory distress syndrome (ARDS), ischemia, impeded and blocked respiration, respiratory distress syndrome (RDS), pain, cystic fibrosis (CF), pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD)].

SUB 07  
M 7

146. (Amended) The aerosol or spray formulation of claim 108, [wherein] which is selected from powders, sprays, solutions, suspensions or emulsions.

SUB 08  
M 8

148. (Amended) The aerosol or spray formulation of claim 108, which is selected from aqueous or alcoholic solutions or suspensions, oily solutions or suspensions, or oil-in-water or water-in-oil emulsions.

SUB 09  
M 9

152. (Amended) The spray or aerosol formulation of claim 146, comprising a solid powdered spray or aerosol.

SUB 010  
M 10

158. (Amended) The formulation of claim 143, which comprises an intrapulmonary, intracavitary or intraorgan liquid or solid powdered formulation of particle size about  $0.5\mu$  to about  $10\mu$ , or about  $10\mu$  to about  $500\mu$ .

SUB 011  
M 11

162. (Amended) The formulation of claim 143, which is a respirable or inhalable formulation [of] comprising a solid powdered or liquid aerosol or spray of particle size about  $0.5\mu$  to about  $10\mu$ .

163. (Amended) A single cell, comprising the nucleic acid of claim 108.

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164. (Amended) A kit for diagnosis or treatment of diseases and conditions associated with hypersensitivity to and/or increased levels of, adenosine and/or bronchoconstriction and/or lung allergy(ies) and/or inflammation and/or asthma comprising, in separate containers,

the delivery device of claim 222;

a nucleic acid comprising at least one oligonucleotide (oligo) effective to alleviate hyper-responsiveness to, and/or increased levels of, adenosine, or to alleviate bronchoconstriction, asthma or lung allergy(ies) and/or inflammation, the oligo being anti-sense to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a gene encoding a protein associated with hyper-responsiveness to, and/or increased levels of, adenosine, with bronchoconstriction, asthma, or lung allergy(ies) or inflammation, or being anti-sense to the corresponding mRNA; the nucleic acid comprising one or more oligo(s), their mixtures or their pharmaceutically or veterinarily acceptable salts [of the oligo(s)]; and

instructions for preparation of a respirable, inhalable, nasal, intrapulmonary, intraorgan, or intracavitary formulation of particle size about 0.5 to about 500  $\mu$  and for its use; and optionally an agent selected from therapeutic or diagnostic agents other than the oligo, anti-oxidants, fillers, volatile oils, dispersants, anti-oxidants, flavoring agents, propellants, preservatives, solvents, buffering agents, RNA inactivating agents, agents that are internalized or up-taken by a cell, or coloring agents.

165. (Amended) The kit of claim 164, wherein the delivery device comprises a nebulizer that delivers single metered doses of a solid powdered or liquid aerosol or spray formulation of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$  of the nucleic acid.

166. (Amended) The kit of claim 164, wherein the device comprises an insufflator adapted for receiving and piercing or opening a capsule(s) or cartridge(s) and producing a solid powdered or liquid aerosol or spray; and the nucleic acid is provided separately in a pierceable or openable capsule(s) or cartridge(s) as a nasal, inhalable, respirable, intrapulmonary, intracavitary or intraorgan formulation of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ .

167. (Amended) The kit of claim 164, wherein the delivery device comprises a pressurized [inhalator] inhaler that delivers a solid powdered or liquid aerosol or spray of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ ; and the nucleic acid is provided as a suspension, solution, emulsion or dry p wder aerosol or spray formulation of about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ .

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SUB 011  
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M11  
cont

168. (Amended) The kit of claim 164, comprising the delivery device, a surfactant, the nucleic acid and other therapeutic agents

[a therapeutic agent selected from adenosine A1, A2b or A3 receptor antagonists other than the oligo(s), adenosine A2a receptor stimulants, anti-inflammatory agents, anti-histaminic agents, anti-allergic agents, anti-bacterial, anti-virals, analgesics, kidney activity maintenance or restoration agents, anti-cancer agents, adenosine, blood pressure controlling agents, or diuretics].

171. (Amended) The kit of claim 164 further comprising, in [a] separate containers, a propellant, and pressurized means for delivery adapted for delivering a solid powdered or liquid aerosol or spray, and instructions for loading into the delivery device the nucleic acid as an inhalable, respirable, nasal, intracavitary, intraorgan or intrapulmonary formulation of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ , and then joining the device with the propellant and the pressurized means.

SUB 012  
M12

172. (Amended) The kit of claim 167, wherein the pressurized [inhalator] inhaler further comprises a propellant and means for delivery of the propellant, and delivers the nucleic acid as a liquid or solid powdered aerosol or spray formulation [of the nucleic acid].

173. (Amended) An in vivo method of delivering a pharmaceutical composition to a target polynucleotide, comprising administering to the airways of a subject an aerosol or spray composition of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10 to about 500  $\mu$  [,] comprising a nucleic acid [which] that comprises at least one oligonucleotide (oligo) effective to alleviate hyper-responsiveness to, and/or increased levels of, adenosine, or to alleviate bronchoconstriction, asthma and/or lung allergy(ies) and/or inflammation, the oligo containing up to and including about 15% adenosine (A), and being anti-sense to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a gene encoding a protein associated with hyper-responsiveness to, and/or increased levels of, adenosine, [with] bronchoconstriction, asthma [,] and/or lung allergy(ies) and/or inflammation, or being anti-sense to the corresponding mRNA; the nucleic acid comprising one or more oligo(s), pharmaceutically [and] or veterinarily acceptable salts of the oligo(s), or mixtures of the oligo(s) or their salts.

SUB 013  
M13

178. (Amended) The method of claim 173, wherein the composition is administered intrapulmonarily, intraorgan, intracavitarily, intrabuccally, intranasally, by inhalation or into the subject's respiratory system.

SUB 014  
M14

181. (Amended) The method of claim 178, wherein the composition is administered as [powdered] solid powdered or liquid particles of the nucleic acid about 0.5 to about 10  $\mu$  in size.

M15  
SUB 015

185. (Amended) The method of claim 173, wherein the hyper-responsiveness to,

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and/or increased levels of, adenosine, [or bronchoconstriction] asthma or lung allergy(ies) or inflammation is associated with bronchoconstriction of lung airways.

186. (Amended) The method of claim 185, wherein the hyper-responsiveness to, or increased levels of, adenosine, [or] bronchoconstriction, asthma or lung allergy(ies) or inflammation is associated with COPD, asthma, ARDS, RDS, CF or side effects of adenosine administration.

187. (Amended) The method of claim 173, wherein the hyper-responsiveness to, or increased levels of, adenosine, [or] bronchoconstriction, asthma, or lung allergy(ies) or inflammation is associated with inflammation or an inflammatory disease.

188. (Amended) The method of claim 173, wherein the composition further comprises other therapeutic agents

[a therapeutic agent selected from adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptor inhibiting agents or adenosine A<sub>2a</sub> receptor stimulating agents other than the nucleic acid(s), anti-inflammatory agents, anti-bacterial agents, anti-sepsis agents, kidney activity maintenance or restoration agents or agents for the treatment of pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome (RDS), acute respiratory distress syndrome (ARDS), pain, cystic fibrosis (CF), pulmonary hypertension, pulmonary vasoconstriction, emphysema, or chronic obstructive pulmonary disease (COPD)].

189. (Amended) The method of claim 188, wherein the therapeutic agent [is selected from] comprises anti-adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptor agents or adenosine A<sub>2a</sub> receptor stimulating agents other than the nucleic acid(s).

191. (Amended) The method of claim 184, wherein the surfactant comprises surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D or active fragments thereof, non-dipalmitoyl disaturated phosphatidylcholine, dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholin, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycerol-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate, lamellar bodies, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitic acid, non-ionic ethylene and/or propylene oxide block copolymers, polyoxypropylene, polyoxyethylene, poly(vinyl amine) with dextran and/or alkanoyl side chains, polyoxy ethylene ethers, phenoxy polyethoxy alcohols, phosphatidyl choline esters, [and] phosphatidyl ethers, palmitates, alcohols

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M16  
cont  
SUB 016  
contand tyloxapol, phospholipids, fatty acids, [or] surfactant-associated proteins, [and] or  $C_{22}H_{19}C_{10}$ .

200. (Amended) The method of claim 173, wherein the nucleic acid is obtained

SUB 017

by

(a) selecting fragments of a target nucleic acid having at least 4 contiguous bases consisting of G or C; and

M17

[(b) obtaining a first oligo 4 to 60 nucleotides long which comprises the selected fragment and has a C and G nucleic acid content of up to and including about 15%; and (c)]

(b) obtaining a second oligo 4 to 60 nucleotides long comprising a sequence [which] that is anti-sense to the selected fragment, the second oligo having an A base content of up to and including about 15%.

SUB 018

M18

206. (Amended) The method of claim 173, wherein if the oligo contains A, at least one A is substituted with a universal base selected from heteroaromatic bases which bind to a thymidine base but have antagonist activity or less than about 0.3 of the adenosine base agonist activity at the adenosine  $A_1$ ,  $A_{2b}$  or  $A_3$  receptors, or heteroaromatic bases which have no activity or have [an] agonist activity at the adenosine  $A_{2a}$  receptor.

SUB 019

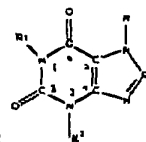
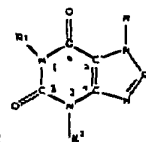
M19

208. (Amended) The method of claim 206, wherein the heteroaromatic bases are selected from pyrimidines [and] or purines [, which] that may be substituted by O, halo,  $NH_2$ , SH, SO,  $SO_2$ ,  $SO_3$ , COOH branched fused primary secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, all of which may be further substituted by O, halo,  $NH_2$ , primary, secondary and tertiary amine, SH, SO,  $SO_2$ ,  $SO_3$ , cycloalkyl, heterocycloalkyl or heteroaryl.

SUB 020

M20

210. (Amended) The method of claim 209, wherein the pyrimidines and purines are selected from theophylline, caffeine, dyphylline, etophylline, acephylline piperazine,

bambifylline, enprofylline or xantine [having the chemical formula , wherein  $R^1$  and  $R^2$  are independently H, alkyl, alkenyl or alkynyl, and  $R^3$  is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl,  $NH_2$ -alkylamino-ketoxyalkyloxy-aryl or mono or dialkylaminoalkyl-N-alkylamino- $SO_2$  aryl].

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SUB 020  
cont  
M 20  
cont

211. (Amended) The method of claim 206, wherein the universal base [is selected from] comprises 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-d] oxazine-7-one or 2-amino-6-methoxyaminopurine.

212. (Amended) The method of claim 173, further comprising methylating at least one cytosine vicinal to a guanosine into a methylated cytosine (<sup>13</sup>C) if a CpG dinucleotide [if] is present in the oligo(s).

SUB 021  
M 21

215. (Amended) The method of claim 173, further comprising operatively linking the nucleic acid to an agent [selected from agents] that enhances cell internalization or up-take, or a cell targeting agent[s].

SUB 022  
M 22

219. (Amended) The method of claim 173, wherein the nucleic acid comprises an oligo [sequence selected from] of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 to SEQ ID NO: 966, or SEQ ID NO: 1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO: 7 to SEQ ID NO: 966, wherein at least one mononucleotide is linked or modified by one or more of phosphorothioate, phosphorodithioate, phosphoromithioate, methylphosphonate, phosphoramidate, boranophosphate, phosphotriester, formacetal, 2'-O-methyl, thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methylimino) (MMI) and methyleneoxy (methylimino) (MOMI), terminal 1,3-propanediol, terminal dodecanol, 2'-O-methoxyethyl, C-5-propynyl pyrimidine, C-5 methyl cytidine, C-5 ethynyl pyrimidine, 2'-propoxy, C-18 amine, N3'-P5' phosphoramidates, 3'-alkylamino, 2'-fluoro; 5-fluoro pyrimidine, 5-iodo pyrimidine, 5-bromo pyrimidine, 2'-borano, C-5 hexynyl pyrimidine, 2'-O-(2-methoxy)ethyl, 2'-O-aminopropyl, 5-(phenylethyl) or peptide nucleic acid interbase linkages or conjugated to a polyethylene glycol, cholesterol, cholesteryl, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEASulfate), dehydroepiandrosterone sulfatide (DHEA Sulfatide), ubiquinone (CoQn), dolichol, poly L-lysine, sulfatidic acid or fatty acids.

SUB 023  
M 23

221. (Amended) The method of claim 173, wherein the hyper-responsiveness to, or increased levels of, adenosine, [or] bronchoconstriction, or lung allergy(ies) or inflammation, is associated with asthma or a disease or condition associated with asthma.

222. (Amended) A diagnostic or therapeutic device adapted for delivering a respirable, inhalable, nasal, intrapulmonary, intraorgan, or intracavitary formulation of particle size about 0.5  $\mu$  to about 500  $\mu$ , the formulation comprising a nucleic acid [which] that comprises at least one oligonucleotide (oligo) effective for diagnosing or treating hyper-responsiveness to, or increased levels of, adenosines, [or] bronchoconstriction, asthma, or lung allergy(ies) or

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inflammation, or a disease or condition associated with either of them, the oligo being anti-sense to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a gene encoding a protein associated with hyper-responsiveness to, or increased levels of, adenosine, bronchoconstriction, asthma, or lung allergy(ies) or inflammation, or being anti-sense to the corresponding mRNA; the nucleic acid comprising one or more oligo(s), their mixtures, or their pharmaceutically or veterinarily acceptable salts.

223. (Amended) The device of claim 222, comprising a nebulizer adapted for delivering single metered doses of the formulation as a solid powdered or liquid aerosol or spray of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ .

224. (Amended) The device of claim 222, which comprises an insufflator adapted for receiving and piercing or opening a capsule(s) or cartridge(s) and for producing a solid powdered or liquid aerosol or spray of particle size about 0.5 $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ , and wherein the formulation is provided separately in a pierceable or openable capsule(s) or cartridge(s) as a nasal, inhalable, respirable, intrapulmonary, intracavitary or intraorgan formulation of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ .

225. (Amended) The device of claim 222, which comprises a pressurized [inhalator] inhaler that delivers a solid powdered or liquid aerosol or spray formulation of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ ; [and] wherein the formulation comprises a suspension, solution, emulsion or dry powder aerosol or spray formulation of the nucleic acid of particle size about 0.05  $\mu$  to about 50  $\mu$  or about 10  $\mu$  to about 500  $\mu$ .

226. (Amended) The pressurized [inhalator] inhaler of claim 225 further comprising, in [a] separate containers, a propellant and pressurized means for delivery[,], adapted for delivering a solid powdered or liquid aerosol or spray, and instructions for loading into [the] the delivery device the inhalable, respirable, nasal, intracavitary, intraorgan or intrapulmonary formulation, and joining the device with the propellant and the pressurized delivery means.

227. (Amended) The pressurized [inhalator] inhaler of claim 225, further comprising a propellant and propellant delivery means, wherein the pressurized [inhalator] inhaler delivers the formulation as a liquid or solid powdered aerosol or spray.

228. (Amended) The device of claim 222, which is adapted for receiving and piercing or opening a capsule(s) or cartridge(s), and wherein the formulation is provided separately in a capsule(s) or cartridge(s).

229. (Amended) The kit of claim 164, wherein the oligo is anti-sense to the initiation codon, the coding region or the 5' or 3' region of a gene encoding a polypeptide selected



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from an adenosine A<sub>1</sub> receptor, adenosine A<sub>2a</sub> receptor, adenosine A<sub>2b</sub> receptor, or adenosine A<sub>3</sub> receptor.

230. (Amended) The kit of claim 229, for diagnosis or treatment of sepsis, pulmonary vasoconstriction, lung inflammation, or allergies, asthma, impeded respiration, respiratory distress syndrome (RDS), acute respiratory distress syndrome (ARDS), pain, cystic fibrosis (CF), pulmonary hypertension, pulmonary vasoconstriction, emphysema or chronic obstructive pulmonary disease (COPD).

231. (Amended) The kit of claim 164, wherein the nucleic acid comprises an oligo [sequence selected from] of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 to SEQ ID NO: 996, or SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO: 7 to SEQ ID NO: 996, wherein at least one mononucleotide is linked or modified by one or more of phosphorothioate, phosphorodithioate, phosphotriethioate, methylphosphonate, phosphoramidate, boranophosphate, phosphotriester, formacetal, 2'-O-methyl, thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methylimino) (MMI) and methyleneoxy (methylimino) (MOMI), terminal 1,3-propanediol, terminal dodecanol, 2'-O-methoxyethyl, C-5-propynyl pyrimidine, C-5 methyl cytidine, C-5 ethynyl pyrimidine, 2'-propoxy, C-18 amine, N3'-P5' phosphoramidates, 3'-alkylamino, 2'-fluoro, 5-fluoro pyrimidine, 5-iodo pyrimidine, 5-bromo pyrimidine, 2'-borano, C-5 hexynyl pyrimidine, 2'-O-(2-methoxy)ethyl, 2'-O-aminopropyl, 5-(phenylethyl) or peptide nucleic acid interbase linkages or conjugated to a polyethylene glycol, cholesterol, cholesteryl, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA Sulfate), dehydroepiandrosterone sulfatide (DHEA Sulfatide), ubiquinone (CoQn), dolichol, poly L-lysine, sulfatidic acid or fatty acids.

234. (Amended) A single cell, comprising the nucleic acid of claim 233.